Applicants respectfully disagree. In a certain embodiment, the present invention as claimed is concerned with methods for the treatment of urinary incontinence by administering the nitro-oxy derivative of indomethacin, that is, (3-nitrooxymethyl)phenyl ester ("NO-indomethacin"). As compared to indomethacin, the NO-indomethacin of the claimed invention is able to provide for several advantages with respect to urinary incontinence. For instance, when administered on the same weight basis as indomethacin, NO-indomethacin is able to provide for a lower frequency of micturition (see Table 2, Examples 4C and 5 at page 52 of the specification), as well as a higher bladder pressure threshold before micturition (see Table 3, Examples 5B and 5 at page 54 of the specification). Also important, as compared to indomethacin, treatment with NO-indomethacin is substantially devoid of side effects for the gastric mucosa such as gastric lesions (see Examples 16-17 and 16A-16B at page 60 of the specification). Applicants note that at the tested dose of 3 mg/Kg, a group tested with the indomethacin compound experienced ulceration in the stomach and intestine, whereas gastric ulcers were observed in only one animal of another group treated with NO-indomethacin (see page 61, lines 5-9 of the specification).

No such invention is taught or suggested in the prior art including the cited references. Applicants note that it is alleged in the Office Action that since the cited references teach indomethacin as old and well known in combination with various pharmaceutical carriers, compounds useful for increasing the time to micturition and increasing bladder pressure would have been seen as useful for treating urinary incontinence. However, Applicants respectfully point out that the claimed invention is concerned with NO-indomethacin rather than the indomethacin of the cited references. Perhaps more important, in light of those unexpected improvements discussed above, the NO-indomethacin of the claimed invention can only be considered non-obvious when compared to the indomethacin of the cited references.

It is also alleged in the Office Action that it would have been obvious to employ an analog, homolog, isomer, bioisostere, salt and ester of a compound for the same therapeutic use. It is further alleged that the prior art use for the same therapeutic purpose would have motivated those of ordinary skill in the art to employ indomethacin esters for the same use with a reasonable expectation of success. Applicants respectfully disagree. It is to be noted that those of ordinary skill in the art are well aware that NO-indomethacin is neither a homolog nor a salt of indomethacin. Moreover, no evidence including any prior art reference has been cited so as to demonstrate that NO-indomethacin is an analog or bioisostere of indomethacin. Applicants note that it is known to those of ordinary skill in the art that NO-indomethacin may qualify as a nitrooxy-ester of indomethacin. Nevertheless, the pharmacological results discussed above clearly demonstrate that it would not have been obvious that such nitrooxy-esters could provide for the unexpectedly improved effectiveness and reduced side effects of the claimed invention.

Finally, as further evidence regarding the non-obviousness of the claimed invention, Applicants submit herein the Declaration of the inventor Dr. Piero del Soldato. The Declaration presents an experimental model of urinary incontinence in rats, wherein volume bladder has been experimentally reduced by former treatment with an acetic acid solution, and administration of the same molar amounts of indomethacin and NO-indomethacin so as to bring about an increase in bladder volume capacity before micturition. In the group treated with the precursor drug indomethacin, the increase in bladder volume capacity after one hour was 26% as compared to the starting bladder volume. Yet, in the group treated with NO-indomethacin of the claimed invention, the increase in bladder volume capacity was much larger at between 66% (30 minutes after

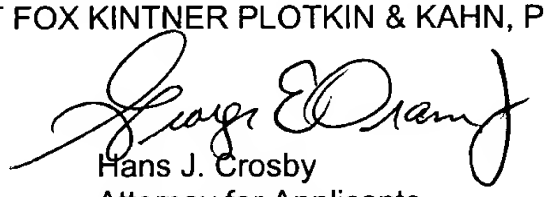
administration) and 59.7% (45 minutes after administration). In other words, not only was the maximum pharmacological effect of NO-indomethacin recorded earlier, but the effect was more that twice that of indomethacin. The compounds of the claimed invention are therefore much more effective in the treatment of urinary incontinence than any precursor indomethacin compound. In other words, in view of such surprising and unexpected improvements in treatment, the compounds of the claimed invention can only be considered non-obvious in view of the teachings of the cited references.

In view of the above remarks, Applicants submit that this application is in condition for allowance and request favorable action thereon.

In the event this paper is not considered to be timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300: The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment associated with this communication to Deposit Account No. 01-2300, referencing Attorney Docket No. 108907-09002.

Respectfully submitted,

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC



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Enclosures: Declaration of Dr. Piero del Soldato

Attorney Docket No. P8907-9002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
P. Del Soldato, et al.) Examiner: Travers Russel
Serial No. 09/147,770) Group Art Unit: 1617
Filed: April 28 1999)
For: NITRIC ESTER DERIVATIVES AND)
THEIR USE IN URINARY INCONTINENCE)
AND OTHER DISEASES)

#23 JRR 8/15/02

DECLARATION OF DR. PIERO DEL SOLDATO

PURSUANT TO 37 C.F.R. § 1.132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, PIERO DEL SOLDATO, do hereby declare that:

1. I am one of the inventors of the invention claimed in the above-identified application Serial No. 09/147,770 ("Application").

2. Under my supervision, direction and control, the following compounds were tested in the pharmacologicalmodel of cystometry in conscious rats:

- Indomethacin.
- The compound indomethacin (3-nitrooxymethyl)phenyl ester, hereinafter called : "indomethacin-NO" prepared as described at pages 45-46 of the pending Application.

Two groups, A and B respectively (n. 8 animals/group) of Sprague Dawley rats (200-300 g body weight) were used. The rats were anesthetised with Nembutal + chlorate hydrate i.p. The abdomen was then opened and the urinary bladder isolated. The bladder was then emptied and cannulated with a polyethylene cannula (Portex® PP30). One day after the catheter implantation the

rats were placed in Bollmann's cages. After a stabilization period of 20 min. the free tip of the cannula was connected to a pressure transducer and to a peristaltic pump. By said pump, at a rate of 0.1 ml/min it was infused a warm (37°C) saline solution into the urinary bladder. The basal bladder volume capacity was thus determined.

Bladder volume capacity (BVC), expressed as ml, is defined as the bladder volume at the time when detrusor contraction is followed by micturition.

It was found to be of 0.66 ml for group A and of 0,63 ml for group B.

Into the bladder was then infused a 0.1% acetic acid solution for 60 minutes to obtain an irritation of the bladder and a reduction of the BVC.. At the end of said period of time the bladder volume capacity in group A was reduced to 0,28 ml and in group B to 0,26 ml. Said values were taken as BVC at t = 0.

Then group A was i.v. administered with indomethacin at a dose of 0.00279 mmole/Kg (1 mg/Kg) and group B with the same amount on a molar basis of indomethacin-NO (1.42 mg/Kg). Infusion with the acetic acid solution was continued for one hour further.

The changes in bladder volume capacity were monitored at 15, 30, 45 and 60 minutes after i.v. administration. Said changes are calculated as % bladder volume capacity changes vs BVC at t = 0.

Results are reported in Table 1.

3. I also declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willfull false statements may jeopardize the validity of the application or any patent or registration issuing thereon.

Table 1

% bladder volume capacity change vs BVC at t = 0 in an experimental model of urinary incontinence by 0.1% acetic acid infusion in the bladder, followed by i.v. administration of a same molar dose (2.79×10^{-3} mmole/Kg) of indomethacin and NO-indomethacin				
Compound	Bladder volume % change following i.v. administration of the compound			
	After 15′	After 30′	After 45′	After 60′
Indomethacin	-16,2%	+ 11,8%	+ 23.9%	+ 26%
NO-indomethacin	+ 53.4%	+ 66%	+ 59.7%	+ 65%

Piero Del Soldato

Date: July 25 2002